Claims

What is claimed is:

1. An injectable particle comprising: 1) a biodegradable polymer; and 2) an NSAID, a local anesthetic, or a narcotic analgesic.

2. An injectable particle comprising: 1) a biodegradable polymer; 2) an NSAID; and 3) a local anesthetic.

3. An injectable particle comprising: 1) a biodegradable polymer; 2) an NSAID; and 3) a narcotic analgesic.

4. An injectable particle comprising: 1) a biodegradable polymer; 2) an NSAID; 3) a local anesthetic; and 4) a narcotic analgesic.

5. An injectable particle comprising: 1) a biodegradable polymer; and 2) an NSAID.

6. An injectable particle comprising: 1) polymer having a backbone, wherein the backbone comprises one or more groups that will yield an NSAID upon hydrolysis of the polymer; and optionally 2) a local anesthetic or a narcotic analgesic.

7. The injectable particle of claim 6 wherein the backbone comprises ester, thioester, amide, anhydride, carbonate or carbamate linkages.

8. The injectable particle of claim 6 wherein the polymer comprises one or more units of formula (I) in the backbone:

$$-R_1\text{-A-L-A-} \qquad \text{(I)}$$

wherein: R_1 is group that will yield an NSAID upon hydrolysis of the polymer; each A is independently an ester linkage, a thioester linkage, or an amide linkage; and L is a linking group.

9. The injectable particle of claim 6 wherein the polymer comprises one or more units of formula (II) in the backbone:

$$-R_2\text{-A-L-A-}R_3\text{-A-L-A-} \qquad \text{(II)}$$

wherein: R_2 and R_3 are each independently a group that will yield an NSAID upon hydrolysis of the polymer; each A is independently an amide or ester linkage; and each L is independently a linking group.

10. The injectable particle of claim 6 wherein the polymer backbone comprises one or more an anhydride linkages.

11. The injectable particle of claim 1 wherein the polymer comprises one or more units of formula (III) in the backbone:

$$-C(=O)R^4\text{-}X\text{-}L\text{-}X\text{-}R^4\text{-}C(=O)\text{-}O- \qquad (III)$$

wherein: each R^4 is group that will provide an NSAID upon hydrolysis of the polymer; each X is independently an amide linkage, a thioester linkage, or an ester linkage; and L is a linking group.

12. The injectable particle of claim 8, 9, or 11 wherein L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 1 to 25 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally replaced by (-O-) or (-NR-), and wherein the chain is optionally substituted on carbon with one or more (e.g. 1, 2, 3, or 4) substituents selected from the group consisting of (C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylthio, azido, cyano, nitro, halo, hydroxy, oxo, carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy.

13. The injectable particle of claim 8, 9, or 11 wherein L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 1 to 25 carbon atoms, wherein the chain is optionally substituted on carbon with one or more (e.g. 1, 2, 3, or 4) substituents selected from the group consisting of (C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylthio, azido, cyano, nitro, halo, hydroxy, oxo, carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy.

14. The injectable particle of claim 8, 9, or 11 wherein L is a peptide.

15. The injectable particle of claim 8, 9, or 11 wherein L is an amino acid.

16. The injectable particle of claim 8, 9, or 11 wherein L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 1 to 25 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally replaced by (-O-) or (-NR-).

17. The injectable particle of claim 8, 9, or 11 wherein L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 3 to 15 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally replaced by (-O-) or (-NR-), and wherein the chain is optionally substituted on carbon with one or more (e.g. 1, 2, 3, or 4) substituents selected from the group consisting of (C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylthio, azido, cyano, nitro, halo, hydroxy, oxo, carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy.

18. The injectable particle of claim 8, 9, or 11 wherein L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 3 to 15 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally replaced by (-O-) or (-NR-).

19. The injectable particle of claim 8, 9, or 11 wherein L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 3 to 15 carbon atoms.

20. The injectable particle of claim 8, 9, or 11 wherein L is a divalent, branched or unbranched, hydrocarbon chain, having from 3 to 15 carbon atoms.

21. The injectable particle of claim 8, 9, or 11 wherein L is a divalent, branched or unbranched, hydrocarbon chain, having 6, 7, or 8 carbon atoms.

22. The injectable particle of claim 8, 9, or 11 wherein L is a divalent hydrocarbon chain having 8, 9, or 10 carbon atoms.

23. The injectable particle of any one of claims 1-22 wherein the NSAID is 3-amino-4-hydroxybutyric acid, aceclofenac, alminoprofen, amfenac, bromfenac, bromosaligenin, bumadizon, carprofen, diclofenac, diflunisal, ditazol, enfenamic acid, etodolac, etofenamate, fendosal, fepradinol, flufenamic acid, gentisic acid, glucamethacin, glycol salicylate, meclofenamic acid, mefenamic acid, mesalamine, niflumic acid, olsalazine, oxaceprol, S-adenosylmethionine, salicylic acid, salsalate, sulfasalazine or tolfenamic acid.

24. The injectable particle of any one of claims 1-22 wherein the NSAID is diflunisal.

25. The injectable particle of any one of claims 1-22 wherein the NSAID is salicylic acid.

26. The injectable particle of any one of claims 1-25 that comprises a local anesthetic.

27. The injectable particle of any one of claims 1-25 that comprises a narcotic analgesic.

28. The injectable particle of any one of claim 26 that comprises a narcotic analgesic.

29. The injectable particle of any one of claims 1-28 wherein the local anesthetic is benzocaine, bupivacaine, butacaine, butanilicane, carticaine, chloroprocaine, cocaine, cyclomethycaine, dibucaine, diperocaine, etidocaine, fomocaine, isobucaine, ketamine, leucinocaine, lidocaine, lignocaine, mepivacaine, meprylcaine, myrtecaine, octacaine, oxybuprocaine, parethoxycaine, phenacaine, piperocaine, pramoxine, prilocaine, procaine, propanocaine, propoxycaine, proxymetacaine, pyrrocaine, ropivacaine, tetracaine, or tolycaine.

30. The injectable particle of any one of claims 1-29 wherein the narcotic analgesic is alfentanil, bremazocine, buprenorphine, butorphanol, codeine, CTOP, [d-Ala^2] deltorphin I, [d-Ala^2, Glu^4] deltorphin (deltorphin II), DADL, DALCE, DAMGO, dihydrocodeine, dihydrocodeinone, diphenoxylate, DPDPE, DSLET, dynorphin A, dynorphin B, endomorphin-1, endomorphin-2, β_h-endorphin, FK-33824, [Leu^5] enkephalin, [Met^5] enkephalin, ethylketocyclazocine, etorphine, fentanyl, heroin, hydrocodone, hydromorphone, levallorphan, levorphanol, meperidine, methadone, morphiceptin, morphine, morphine-6-glucuronide, nalbuphine, α-neoendorphin, β-neoendorphin, orphinan FQ/nociceptin, PL-017, oxycodone,

oxymorphone, pentazocine, propoxyphene, remifentanil, spiradoline, sufentanil, tramadol, U50,488, or U69,593.

31. The injectable particle of any one of claims 1-30 wherein the local anesthetic is mixed into the polymer so as to achieve a concentration of from 0.1% to about 10% by weight.

32. The injectable particle of any one of claims 1-31 wherein the local anesthetic is present as the free base or as a suitable pharmaceutical salt (e.g., sulfate, phosphate, acetate, tartrate, hydrochloride, etc.).

33. The injectable particle of any one of claims 1-32 wherein the narcotic analgesic is mixed into the polymer so as to achieve a concentration of from 1% to about 30% by weight.

34. The injectable particle of any one of claims 1-33 wherein the narcotic analgesic is present as the free base or as a suitable pharmaceutical salt (e.g., sulfate, phosphate, acetate, tartrate, hydrochloride, etc.).

35. The injectable particle of any one of claims 1-34 wherein the local anesthetic is mixed into the polymer so as to achieve a concentration of from 0.1% to about 10% by weight, and the narcotic analgesic drug is mixed into the polymer so as to achieve a concentration of from 1% to about 20% by weight.

36. The injectable particle of any one of claims 1-35 wherein the local anesthetic and the narcotic analgesic drug are present as free bases or as suitable pharmaceutical salts (e.g., sulfate, phosphate, acetate, tartrate, hydrochloride, etc.).

37. The injectable particle of any one of claims 1-36 that has a maximum dimension of from about 0.001 microns (micrometers) to about 100 microns.

38. The injectable particle of claim 37 wherein the maximum dimension is determined by dynamic light scattering.

39. The injectable particle of any one of claims 1-38 that is a microsphere.

40. The microsphere of claim 39 that has a diameter of from about 0.001 microns (micrometers) to about 100 microns.

41. The microsphere of claim 40 wherein the diameter is determined by dynamic light scattering.

42. The injectable particle of any one of claims 1-41 wherein the local anesthetic is lidocaine.

43. The injectable particle of any one of claims 1-42 wherein the narcotic analgesic is morphine.

44. A microsphere comprising: 1) polymer having a backbone, wherein the backbone comprises one or more groups that will yield salicylic acid or diflunisal upon hydrolysis of the polymer; and optionally 2) lidocaine or morphine.

45. A microsphere comprising: 1) polymer having a backbone, wherein the backbone comprises one or more groups that will yield salicylic acid or diflunisal upon hydrolysis of the polymer; and 2) lidocaine.

46. A microsphere comprising: 1) polymer having a backbone, wherein the backbone comprises one or more groups that will yield salicylic acid or diflunisal upon hydrolysis of the polymer; and 2) morphine.

47. A microsphere comprising: 1) polymer having a backbone, wherein the backbone comprises one or more groups that will yield salicylic acid or diflunisal upon hydrolysis of the polymer; 2) lidocaine; and 3) morphine.

48. A pharmaceutical composition comprising a plurality of injectable particles as described in any one of claims 1-47 and a pharmaceutically acceptable carrier.

49. The composition of claim 48 that is formulated for i.a. injection.

50. A method for treating RA in a mammal comprising administering to the mammal, an effective amount of the injectable particles described in any one of claims 1-47.

51. A method for treating RA in a mammal comprising administering to the mammal, an effective amount of a composition as described in any one of claims 48-49.

52. The method of claim 51 wherein the composition is administered i.a. to the site of the RA.

53. The injectable particles as described in any one of claims 1-47 for use in medical therapy.

54. A method for treating spinal stenosis, bursitis, tendonitis, epicondylitis, fibromyalgia, chronic foot and ankle pain, calcaneal spur syndrome, neuralgia, metatarsalgia, metatarsophalangeal articulation, or osteoarthritis in a mammal comprising administering to the mammal, an effective amount of the injectable particles described in any one of claims 1-47.

55. A method for treating spinal stenosis, bursitis, tendonitis, epicondylitis, fibromyalgia, chronic foot and ankle pain, calcaneal spur syndrome, neuralgia, metatarsalgia, metatarsophalangeal articulation, or osteoarthritis in a mammal comprising administering to the mammal, an effective amount of a composition as described in any one of claims 48-49.

56. A method to prevent or reduce swelling of central nervous system tissues in a mammal comprising administering to the mammal, an effective amount of the injectable particles described in any one of claims 1-47.

57. A method to prevent or reduce swelling of central nervous system tissues in a mammal comprising administering to the mammal, an effective amount of a composition as described in any one of claims 48-49.

58. A method to inhibit inflammatory response of the nervous system or surrounding tissue following injury in a mammal comprising administering to the mammal, an effective amount of the injectable particles described in any one of claims 1-47.

59. A method to inhibit inflammatory response of the nervous system or surrounding tissue following injury in a mammal comprising administering to the mammal, an effective amount of a composition as described in any one of claims 48-49.

60. The composition described in claim 48 or 49 for use in medical therapy.

61. The use of an injectable particle as described in any one of claims 1-47 for the manufacture of a medicament useful for the treatment of a RA in a mammal.

62. The use of an injectable particle as described in any one of claims 1-47 for the manufacture of a medicament useful for the treatment of spinal stenosis, bursitis, tendonitis, epicondylitis, fibromyalgia, chronic foot and ankle pain, calcaneal spur syndrome, neuralgia, metatarsalgia, metatarsophalangeal articulation, or osteoarthritis in a mammal.

63. The use of an injectable particle as described in any one of claims 1-47 for the manufacture of a medicament useful to prevent or reduce swelling of central nervous system tissues in a mammal.

64. The use of an injectable particles as described in any one of claims 1-47 for the manufacture of a medicament useful to inhibit inflammatory response of the nervous system or surrounding tissue following injury in a mammal.

65. The composition of claim 48 that is formulated for systemic administration.

66. The composition of claim 48 that is formulated for local injection at a site of pain or inflammation in a mammal.